IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re Application of	)	
	)	FOR: METHODS FOR DETECTING
JUDITH A. VARNER	)	AND INHIBITING
	)	ANGIOGENESIS
Serial No.: 09/307,223	)	
	)	Group
Filed: May 7, 1999	)	Art Unit: 1646

RESPONSE TO RESTRICTION REQUIREMENT UNDER 37 C.F.R.§ 1.143

Hon. Assistant Commissioner for Patents
Washington, D.C. 20231

Attention: Susan Unger, Ph.D.
Primary Patent Examiner

Dear Sir:

This communication is in response to the Office Action dated May 7, 2000. Enclosed herewith is a check for the appropriate fee for a four (4) month extension of time for response.

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I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner of Patents and Trademarks, Washington, D.C. 20231 on:

October 10, 2000
(Mailing Date)

Eleanor M. Musick
(Registered Representative)

Eleanor M. Musick
(Signature)

October 10, 2000
(Date of Signature)

[RESRVARN00.J05]

In the subject Office Action, the Examiner requires restriction of the invention under 35 U.S.C. §121 to one of the following groups:

I. Claims 1-20, 55-75, which the Examiner characterizes as drawn to a method of reducing or inhibiting angiogenesis;

II. Claims 21-34, which the Examiner characterizes as drawn to a method of identifying the presence of angiogenesis in a tissue;

III. Claims 35-46, which the Examiner characterizes as drawn to an *in vitro* method of diagnosing a pathological condition;

IV. Claims 47-54, which the Examiner characterizes as drawn to an *in vivo* method of diagnosing a pathological condition; and

V. Claims 76-79, which the Examiner characterizes as drawn to a method of identifying an agent that reduces or inhibits angiogenesis.

In response to this restriction requirement, and without admitting the correctness of the Examiner's groupings, Applicant hereby provisionally elects Claims 1-20, 55-75 drawn to a method of reducing or inhibiting angiogenesis (Group I) for examination of this application.

Notwithstanding the above election of Group I, Applicant traverses the restriction requirement and asks that the Examiner reconsider the grouping of the claims. Specifically, Applicant requests the regrouping of Groups I, II and V with at least the regrouping of Groups I and V. The Examiner contends that the five groupings of inventions are recognized as divergent in the art, referencing separate classifications, on the basis that the five groupings exist as materially distinct methods which differ at least in objectives, method steps, reagents and/or dosages and/or schedules used, response variables, and criteria for success.

As to the separate classification, it has long been recognized that separate classification alone is not acceptable grounds for artificially partitioning a unitary invention; *Ex Parte Goldsmith*, 155 U.S.P.Q. 107 (P.T.O.Bd.App., 1966). The Board specifically stated in *Goldsmith* that the PTO's classification system is merely a

convenience for examiners for organizing searches, and is not a statement of art-recognized categorization of technology.

As to the alleged materially distinct methods, differing objectives, method steps, reagents/dosages/schedules, response variables, and criteria, it should be recognized that the method drawn to reducing or inhibiting angiogenesis in tissue, the method of identifying angiogenesis in tissue, and the method of identifying an agent that reduces or inhibits angiogenesis in tissue are closely related aspects of the same invention, and as such, will require virtually identical fields of search. Within the separate groupings, specifically within the method steps of Groups I, II and V, the stated objective is to the same end - the reduction or inhibition of angiogenesis in a tissue. There is little divergence between method steps for identifying angiogenesis in a tissue (Group II) and reducing or inhibiting angiogenesis in a tissue (Group I). Both involve contacting of $\alpha 5\beta 1$ integrin in the tissue with an agent that interferes with the specific binding of the $\alpha 5\beta 1$ integrin to a ligand. Angiogenesis associated with $\alpha 5\beta 1$ integrin expression can occur locally as in the case of diabetic retinopathy or systemically as in the case of malignant neoplasm. Similarly, identifying an agent that reduces or inhibits angiogenesis in a tissue (Group V), as well, involves the reduction or interference of specific binding of $\alpha 5\beta 1$ integrin to a ligand through contacting of $\alpha 5\beta 1$ integrin present in the tissue with the agent in question. The method steps of Groups II and V can involve detectably labeling the agent, for example, by linking it to an X-ray attenuating material, however such *in vivo* testing is clearly defined within the classification assigned to the groupings by the Examiner.

In the assignment of groupings, the Examiner has designated Group I as defined within Class 424, subclass 130.1 and Class 514, subclass 2; Group II as defined within Class 424, subclass 130.1 ad Class 514, subclass 2; Group III as defined within Class 435, subclasses 4 and 7.1; Group IV as defined within Class 424, subclass 130.1 and Class 514, subclass 2; and Group V as defined within Class 514, subclass 2 and Class 435, subclass 4. Broadly defined, Class 424 includes subject

matter related to drugs and bio-affecting and body treating compositions for preventing, alleviating, treating, or curing abnormal and pathological conditions of the living body (*e.g.* angiogenesis). Class 424 also includes the diagnosis of physiological conditions or states using ***in vivo*** test means. Further, the subclassification 130.1 provides for bioaffecting and body treating compositions comprising immunoglobins, antisera, antibodies or antibody fragments.

Also cited by the Examiner, Class 514 is an integral part of Class 424 and as such incorporates all the definitions and rules as subject matter of Class 424. Subclasses 1-768 of Class 514 provide for the subject matter proper under Class 424 containing a designated organic active ingredient (DOAI), methods of making such composition and methods of using such composition. Also included herein are method of using a specified DOAI. Subclass 2 is specific for subject matter which contains a protein, peptide, peptone, fibrinogen, etc. as a designated organic active ingredient.

In the third classification grouping cited by the Examiner, Class 435, broadly, provides for processes of using microorganisms or enzymes to synthesize a chemical product; treat a material to liberate or purify a preexisting product. More specifically, Class 435 is used to define ***in vitro*** processes of measuring and testing involving the use of microorganisms or enzymes to determine the presence or identity of a compound or composition in a sample. The subclassifications cited by the Examiner, 4 and 7.1, define processes in which there is a direct or indirect qualitative or quantitative measurement or test of a material which contains an enzyme or microorganism or processes in which a material containing an enzyme or microorganism is used to perform a qualitative or quantitative measurement and the process of making such a composition, and subject matter in which a measurement or test utilizes an enzyme or microorganism or plant or animal cells in an antibody binding, specific binding protein or other specific ligand-receptor binding test or assay, respectively.

On the basis of these classification definition guidelines provided by the PTO,

the claims of Groups I, II, IV and V clearly all fall within the defined subject matter of Class 424 covering the use of ***in vivo*** body treating compositions, including the use of antibodies, and ***in vivo*** diagnosis of pathological conditions, and the closely related Class 514 covering the use of designated organic active ingredients, including peptide and small organic molecule agents, for the ***in vivo*** treating and/or diagnosis of pathological conditions. The methods steps contained within the claims of Groups I, II and V are materially similar with identical objectives and criteria for success - the reduction or inhibition of angiogenesis in a tissue. As such, Applicant contends that a prior art search within the defined subject matter, covering the above stated aspects of the claims within Groups I, II and V, with at least the claims within Groups I and V, would not pose an unreasonable burden upon the Examiner. This is further supported through the review of issued U.S. Patent No. 6,099,823 with claims drawn to methods and compositions for the treatment and diagnosis of disorders associated with angiogenesis. Thereby Applicant request the recombining of Groups I, II and V, or at least the Groups I and V, and the claims contained therein.

In response to the Examiner's further division of species within the Groups I-V, Applicant traverses the Restriction Requirement and offers the following arguments and support in favor of recombination.

Examiner contends that Group I is further subject to election of a number of single disclosed species wherein the species comprises 1) tissues with different structures and function including, (a) ocular tissue; (b) skin tissue; (c) synovial tissue; (d) bone tissue; (e) neoplastic tissue, and joints; 2) pathological conditions wherein the conditions have different etiologies, wherein the conditions are (a)(i) diabetic retinopathy, (a)(ii) macular degeneration; and 3) neoplasms with different etiologies comprising (e)(i) benign neoplasm, (e)(ii) a malignant neoplasm, including a carcinoma, (e)(iii) metastatic malignant neoplasm, (e)iv) a sarcoma, (e)(v) a mesothelioma, (e)(vi) a teratocarcinoma, (e)(vii) an astrocytoma and, (e)(viii) a glioblastoma . In response, Applicant respectfully points out that Group I and the inclusive claims are drawn to a

method of reducing or inhibiting angiogenesis in tissue. By definition, angiogenesis is a process whereby new blood vessels are formed in tissue in response to stimulation by growth factors causing normally non-proliferative endothelial cells (the cells that form and line the lumen of all veins, arteries, arterioles and capillaries) to become activated and begin to proliferate and migrate into unvascularized tissue to form new blood vessels. Angiogenesis occurs in a variety of pathological conditions. In the case of many types of ocular diseases and cancers, ischemic conditions result in the neovascularization of the effected tissue. In the ocular diseases, diabetic retinopathy and macular degeneration, the formation of fragile blood vessels within the retina result in the loss of vision due to the weak vessels breaking thereby allowing the leakage of fluid and blood within the eye . In many cancers, blood vessel formation in the growing tumor provides oxygen and nutrients to the tumor cells allowing their growth and subsequent metastasis into other area of the body. Conditions associated with tissue inflammation such as rheumatoid arthritis and inflammatory bowel disease are also the result of abnormal neovascularization within the tissue.

Blood vessels are surrounded by extracellular matrix. In addition to stimulation by growth factors, angiogenesis depends on interaction of the endothelial cells with the extracellular matrix. The activation of endothelial cells by growth factors and the migration into and interaction with the extracellular matrix and with each other is dependent on cell surface receptors expressed by the endothelial cells. The process of endothelial cell migration is functionally identical in all tissues. These cells surface receptors, which include growth factor receptors and integrins, in the case of the instant invention $\alpha 5\beta 1$ integrin, interact specifically with particular molecules. Integrins are cell surface adhesion and signaling molecules that mediate the adhesion of cells to the extra cellular matrix.

Given that angiogenesis involves the activation of endothelial cells, in response to stimuli, to cause the formation of blood vessels, angiogenesis can occur in a wide variety of tissues regardless of type or location in the body or in any type of cancer

where the formation of blood vessels provide the growing tumor with oxygen and nutrients. As taken from Essential Cell Biology: An Introduction to the Molecular Biology of the Cell; Garland Publishing, Inc.; New York, London, "Although the specialized tissues in our body differ in many ways, they all have certain basic requirements, usually provided for by a mixture of cell types... All tissues need mechanical strength, which is often supplied by a supporting bed or framework of connective tissue inhabited by fibroblasts. This connective tissue combines with endothelial cells to form blood vessels that function to satisfy the need for oxygen, nutrients, and waste disposal....". As such, the contention that the combination of claims drawn to a method of reducing or inhibiting angiogenesis in a) ocular tissue; b) skin tissue; c) synovial tissue; d) bone tissue; e) neoplastic tissue, and joints represent a plurality of disclosed patentably distinct species is not applicable. The Examiner is requested to consider U. S. Patent No. 5,766,591, with claims drawn to methods for inhibiting angiogenesis occurring in several different tissues as a result of a number of different conditions. This patent helps illustrate the common thread of the desired inhibition of angiogenesis as it occurs through many different tissue types and conditions.

As to differing etiologies cited by the Examiner in the claims drawn to pathological conditions such as (a)(i) diabetic retinopathy and (a)(ii) macular degeneration and in the claims drawn to neoplasms comprising (e)(i) benign neoplasm, (e)(ii) a malignant neoplasm, including a carcinoma, (e)(iii) metastatic malignant neoplasm, (e)iv) a sarcoma, (e)(v) a mesothelioma, (e)(vi) a teratocarcinoma, (e)(vii) an astrocytoma and, (e)(viii) a glioblastoma, the argument against the separation of claims by species is similar to that proposed above. The term neoplasm is synonymous with the term tumor. A tumor is any abnormal proliferation of cells, which may be either benign or malignant. Both benign and malignant tumors are classified according to the type of cells from which they arise. Most cancers fall into one of three main groups: carcinomas, sarcomas, and lymphomas (leukemia). Carcinomas are malignancies of

epithelial cells. Sarcomas are solid tumors of connective tissues such as muscle, bone, cartilage, and fibrous tissue. Lymphomas and leukemia arise from blood-forming cells and from cells of the immune system. All types of neoplasms (*i.e.* tumors) rely on the formation of blood vessels (angiogenesis) to provide the proliferating cells with oxygen and nutrients and then as a pathway for metastasis throughout the body. Therefore, the differing etiologies as claimed by the Examiner should in fact be categorized as a single disclosed species. The same argument applies to diabetic retinopathy and macular degeneration. While the clinical definition of these two conditions vary slightly, the underlying cellular processes resulting in a loss of vision is identical. According to the National Eye Institute, individuals diagnosed as having diabetic retinopathy often develop a condition called macular edema. This occurs when tiny blood vessels formed in the retina become damaged, leaking fluid and lipids onto the macula. As the disease progresses, the fragile, new blood vessels grow along the retina and in the clear, gel-like vitreous that fills the inside of the eye. Without timely treatment, these new blood vessels can leak, cloud vision, and destroy the retina. Similarly, in age-related macular degeneration, new blood vessels behind the retina start to grow toward the macula. Because, as with diabetic retinopathy, these new blood vessels are very fragile, they often leak blood and fluid under the macula. This causes rapid damage to the macula that can lead to the loss of central vision within a short period of time. As such, the differing etiologies as claimed by the Examiner should in fact be categorized as a single disclosed species.

In support of Applicant's argument that the biological mechanisms involved in the neovascularization of varying tissues and pathological conditions, hence angiogenesis, does not vary significantly between tissue types or pathological etiologies, and thus need not be separated by species as contended by the examiner, Applicant further cites U.S. Patent Nos. 6,040,311 and 6,028,061 as containing claims drawn to methods of inhibiting angiogenesis in a wide variety of tissue types and pathological etiologies. Given the previous issuance of patents claiming a wide

variety of tissues and pathological etiologies, Applicant contends that a prior art search within the defined subject matter, covering the above stated aspects of the claims within Groups I would not pose an unreasonable burden upon the Examiner.

The Examiner further requires an election of species within the claims of Group I with regard methods of administration and dosage, wherein the methods comprise (a) administered as eye drops, (b) administered I.V., (c) administered orally, and (d) administered intraneoplasm. Applicant refers to existing U.S. Patent No. 5,766,591 as having claims drawn to intravenous, transdermal, intramuscular, topical, subcutaneous and peristaltic administration of an integrin antagonist for the inhibition of neovascularization of a solid tumor tissue. Additionally in the '591 patent, are claims drawn to different dosing regimes ("one or more dose administrations daily for one to several days" or "a single dose") for the administration of the said antagonist. U.S. Patent No. 6,028,061 contains claims drawn to both topical application to the skin and application to the eye for the administration of an angiogenesis inhibitory molecule. Given the existence of current U.S. Patents wherein claims are drawn to a wide variety of administration means and dosage schedules, Examiner's contention that differing methods of administration comprise patentably distinct species is not correct. A search of the relevant art would not pose an unreasonable burden on the Examiner.

In response to the further restriction of species relating to agents having different structures and functions wherein the agent comprises (a) a peptide, (b) an antibody, and (c) a non-peptide organic molecule, Applicant hereby provisionally elects those claims drawn to (a) a peptide, for examination of this application.

Notwithstanding the above election of (a) a peptide, Applicant traverses the restriction requirement and asks that the Examiner reconsider the species grouping where it relates to agents ((a) a peptide, (b) an antibody, and (c) a non-peptide organic molecule) for the reduction or inhibition of angiogenesis. Applicant cites U.S. Patent No. 6,099,823 as having claims drawn to a number of agents as substances to be

tested for an ability to ameliorate symptoms of a fibroproliferative disease. The claimed substances include an oligonucleotide (claim 7), an anti-sense or ribozyme molecule (claim 8), a small organic or inorganic molecule (claim 9), and an antibody (claim 11). While the peptide, antibody and non-peptide small molecule antagonists of the instant invention vary in structure, they remain identical as to objectives, method steps, dosages and/or schedules used, response variable, and criteria for success. Given the '823 patent as having claims drawn to multiple agent antagonists and the lack of material distinctness between the agent antagonists of the instant invention, the requirement of an election of a single species would not be proper.

Examiner has further subjected Group V to election of a single disclosed species. Claims 76-79 (Group V) are to a method of identifying an agent that reduces or inhibits angiogenesis associated with $\alpha 5\beta 1$ integrin expression in a tissue, wherein contacting the tissue occurs *in vivo* and/or *ex vivo*. The Examiner has assigned the claims of Group V to Class 435, subclass 4 and Class 514, subclass 2. In accordance with the U.S. Patent Classification System - Classification Definitions, Class 435 provides for the following subject matter:

A. A process for using a microorganism or enzyme to synthesize a chemical product;

B. A process of treating a material with a microorganism or enzyme to separate, liberate, or purify a preexisting substance;

C. An *in vitro* process of measuring and testing in which: (1) A microorganism or enzyme is used to determine the presence or identity of a compound or composition in a sample; (2) A microorganism is identified by propagation; (3) An enzyme is identified by its catalytic activity; (4) The presence of microorganisms is detected; (5) A live organism is used in an antigen antibody test as an antigen; (6) Fixed or stabilized nonliving microorganisms, cells, or tissues are involved.

Clearly, the assignment of Class 435, to *in vitro* processes of measuring and testing, is in error as the claims of Group V are drawn only to methods comprising contacting

tissue *in vivo* and *ex vivo* and not *in vitro* as defined by Class 435. Therefore, the election of species should not be applicable.

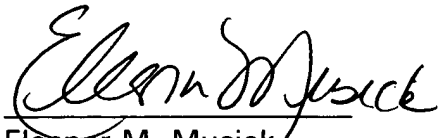
It is submitted, with the above referenced evidence, that the various species cited by the Examiner are not patentably distinct and as such do not require separate election. This case clearly falls within the provisions of M.P.E.P. §803, second paragraph, requiring that the Examiner examine the entire application on its merits where such would effectively minimize the search effort. Therefore withdrawal of the restriction requirement and further election of single disclosed species and examination of Claims 1-34, 55-79 in this application is believed appropriate under the USPTO's procedures and is such respectfully requested.

In the event that the Examiner elects to maintain the restriction requirement, Applicant reserves their right under 35 U.S.C. §121 to file one or more divisional applications covering the subject matter of non-elected Claims 35-54.

Should the Examiner believe that the prosecution of this application might be expedited by further discussion of the issues, she is cordially invited to telephone the undersigned attorney for applicant, collect, at the telephone number listed below.

Respectfully submitted,

Dated: October 10, 2000

By: 

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